of a Terminal Disclaimer would moot the rejection. Accordingly, it is requested that the rejection be held in abeyance until the case is otherwise in condition for allowance.

Claims 33, 37 and 42-48 stand rejected under 35 USC 112, first paragraph. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

As Applicants understand it, the Examiner's position can be summarized as follows:

i) fFor the treatment of humans, it is essential to use humanized antibodies whereas the present specification makes no mention of this; and

ii) the present specification only refers specifically to rheumatoid arthritis and multiple sclerosis as autoimmune conditions and apart from a lack of enablement for autoimmune conditions generally, Schmidt et al shows that anti-CD4 antibodies are not effective in the treatment of MS.

Applicants respectfully disagree.

Insofar as the alleged necessity of using humanized antibodies is concerned ((i) above), the Examiner's attention is again directed to the Declaration of Dr. Scott Crowe dated July 7, 1995, specifically, section 7. The content of that section will not be repeated in its entirety here but emphasis of the following points is believed appropriate as they make clear

the fact that it is not correct to draw the conclusion that rodent antibodies cannot be used for therapy in humans:

i) a number of the antibodies in development listed in Exhibit JSC 1 are rodent antibodies (Declaration paragraph 7.4);

ii) marketing approval had been granted for the mouse monoclonal antibody PANOREX (Declaration paragraph 7.3);

iii) the possibility of a HAMA response must always be borne in mind but this has not been sufficient to deter development of rodent antibodies (Declaration paragraph 7.5);

iv) while a serious anti-idiotype response has the potential to render any antibody unusable, in practice this does not generally happen although antibody therapy will always include monitoring for such a response (an anti-idiotype response can apply equally with a humanized antibody) (Declaration paragraph 7.6);

v) Bach et al suggest that academic groups should carry out initial clinical studies using rodent antibodies (Declaration paragraph 7.9); and

vi) an important reason why pharmaceutical companies prefer humanized or chimeric antibodies is that they are recombinant proteins so that control over production and purification is easier - this has nothing to do with therapeutic efficacy (Declaration paragraph 7.9).

It is respectfully submitted that the foregoing points refute completely the Examiner's assertion that "Crowe appears to rely on the use of chimeric or humanized antibodies to alleviate the limitations of antibody therapy in humans". Indeed, Dr. Crowe went to some lengths in his Declaration to explain that therapy with rodent antibodies is quite feasible.

If, in making his assertion, the Examiner is be referring to OKT3, discussed by Dr. Crowe in Declaration paragraph 7.7, it is important that the Examiner remember that this paragraph commences with the statement that:

> "It is generally possible to live with the responses discussed above in the development of antibody therapy in the sense that they can be controlled if they arise and therapy continued."

Dr. Crowe then refers to the possibility that the antibody can be engineered and refers to the case of OKT3. It is interesting to note that the main reason for engineering in the case of OKT3 was to reconstruct the Fc region. In fact, it was only incidentally that it was decided to humanize the antibody at the same time.

The fact that the work reported in the abstracts in the Arthritis and Rheumatism reference all used humanized or primatized antibodies simply reflects the antibodies that the groups in question happened to be working with. It is not evidence that rodent antibodies cannot be used therapeutically. Abstracts 1300, 1301 and 1302 relate to work from Glaxo Wellcome.

Since the non-depleting anti-CD4 antibody that Glaxo Wellcome has in development is a humanized antibody, it is hardly surprising that these abstracts relate to work on a humanized antibody. This is evidence only of the nature of the antibody that Glaxo Wellcome has in development, not evidence that a humanized antibody is essential for use in therapy in man. Similarly, Abstract 574 is evidence only as to the nature of the antibody that IDEC/SB has in development. That humanized antibodies may now be preferred for therapy in humans in no way supports the assertion that the subject specification fails to enable use of rodent antibodies.

In addition to the above, it is noteworthy that use of rodent antibodies in the case of therapy with an anti-CD4 antibody may well be more feasible that with other types of antibodies as the anti-CD4 antibody also includes immunological unresponsiveness to itself. Thus, the adverse reactions relied on by the Examiner are likely to be less of a problem with an anti-CD4 antibody.

Turning to use of non-depleting anti-CD4 antibody in MS (point (ii) above), the Examiner appears to be suggesting that the Schmidt et al paper shows that non-depleting anti-CD4 antibodies are ineffective in treating MS. Respectfully, this is not a correct interpretation of the reference. As yet, Glaxo Wellcome has carried out Phase I clinical trials with their non-

depleting anti-CD4 antibody in MS and as far as Glaxo Wellcome is aware, no one else with such an antibody in development has gotten any further. As the Examiner is aware, Phase I trials are carried out on a small number of patients and the main purpose is to give a preliminary indication of safety. The number of patients involved is usually too small to provide any statistically significant results as to efficacy. This is the position with MS and it is exactly what Schmidt et al is saying.

The Examiner states on page 4 of the Action:

> "Schmidt et al … disclose that there is no indication for the treatment of multiple sclerosis with monoclonal anti-T cell antibodies at the present time".

The next sentence of the Action is unclear but it is believed the Examiner intended that the specification refers to two autoimmune conditions, one of which (RA) can be treated with non-depleting anti-CD4 antibodies and the other (MS) cannot, but it does not

distinguish between them. If this was the Examiner's intention, respectfully, it is not well founded.[1]

Referring to the final sentence of the abstract, the Examiner appears to have omitted four crucial words which change the meaning of the sentence -- these words are "except in controlled trials". Accordingly, the sentence does not mean (as the Examiner would appear to contend) that there are no circumstances in which treatment of MS with monoclonal anti-T cell antibodies would be appropriate. On the contrary, adding back in the omitted words, the sentence means "the only circumstances in which treatment of MS with monoclonal anti-T cell antibodies would be appropriate is in controlled trials". Bearing in mind the fact that only Phase I trials have as yet

[1] The Schmidt et al paper is in German and the Examiner has provided a translation. Respectfully, Applicants have doubts about the accuracy of the translation. The problems with the translation can be illustrated from the abstract. The final sentence of the abstract (which seems to be the critical one relied on by the Examiner) has the word MS in it but that term is not present in the translation. More importantly, the words "klinischer Studien" have been translated as "controlled trials". The correct translation is "clinical studies" (or possibly "clinical trials"). There is a similar problem in the final sentence of the article at page 17 of the translation where the last words have also been translated as "controlled trials". The German is "experimenteller Studien", whereas the correct translation is "experimental studies". Finally, the translation of the final sentence of the abstract totally omits the abbreviation "z.Z.", short for "zur Zeit" and means "at present". The translation of the final sentence of the paper does translate "z.Z." as "presently" which often does mean the same as "at present".

been carried out, this is unexceptionable and indeed is a statement of that which is self evident.

Several further points relating to Schmidt et al are believed worthy of note:

Page 2, lines 1 to 12 - this provides the theoretical justification for the use of anti-CD4 antibodies in MS (the idea is to eliminate "pathogenic T-cells").

Page 2, line 11 to page 3, line 5 - only Phase I studies are mentioned (since, as indicated above, this is all that there have been so far).

Page 7, lines 1 to 10 (below the figure legend) - further theoretical justification for use of anti-CD4 antibodies in MS.

Page 10, Table 4 - the first two antibodies are anti-CD4 antibodies (although they are both depleting) and in both cases there is some effect on the population of CD4+ T-cells (so that the antibody is doing something in the patient).

Page 12, final sentence - this experiment in the mouse is further evidence that anti-CD4 antibodies are worth looking at in MS.

Page 14, lines 23 to 26 - the fact that allergenic or anaphylactic reactions did not occur is encouraging as is delayed lesion development. The fact that there is no statistically significant decrease in clinical score is <u>not</u> surprising since this was a Phase I trial and, as indicated above, Phase I trials

are not set up to provide a statistically significant demonstration of efficacy. This would come from the "controlled trials" which is the way in which Schmidt et al is suggesting that the antibodies should be used.

Page 15, lines 14 to 16 - the fact that in five patients after 9 months there was no longer an active phase present is also encouraging.

Summarizing far from showing that non-depleting anti-CD4 antibodies are ineffective in MS, Schmidt et al shows the following:

- there is a good basis in theory and in animal studies for expecting that non-depleting anti-CD4 antibodies will be effective in MS

- as yet only Phase I studies have been completed in man; these have not (and were not designed to) provided statistically significant evidence of efficacy but the results are encouraging

- further use of the antibody should be in controlled studies.

In view of the above, the Examiner is urged to reconsider his position. It is believed that, having done so, the Examiner will find withdrawal of the rejection to be in order.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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